REMARKS

The tile of the application has been amended to recite "Preparations for the Promotion of Wound Healing in the Upper Respiratory Tract and/or Ear".

Upon entry of this amendment, claims 54-78 will be pending and under consideration.

Claims 1-53 have been canceled without prejudice in this application and new claims 54-78 have been added to more distinctly claim the invention disclosed in the specification. Support for the newly added claims is as follows:

Claim	Support in Specification
54	page 1, lines 6-11; page 6, line 11 to page 7, line 2
55	page 10, lines 1-3
56	page 10, lines 11-14
57, 58	page 10, lines 22-27
59	page 5, lines 25-27
60-63	page 9, lines 3-7 and claim 10 as originally filed
64-66	page 12, line 25 to page 13, line 6
67, 68	page 8, lines 27-33
69	page 13, lines 11-28
70	page 23, line 9
71	page 24, line 13
72, 73	page 5, line 10
74	page 1, line 11
75, 76	page 4, line 28 to page 5, line 7
77	page 6, line 11 to page 7, line 2
78	page 1, lines 6-11; page 6, line 11 to page 7, line 2

No new matter is added by the amendments to the specification or claims.

1. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 25, 26, 29-47 and 51-53 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. In particular, the Examiner states that the specification "while being enabled for liposomes containing povidone iodine, does not

reasonably provide enablement for generic wound healing agent and anti-septic agent combined with a particulate carrier or various particles . . .".

Applicants note that the claimed invention, as amended, is directed to a method for suppressing undesired tissue formation or for restoring the original appearance of tissue (or suppressing scar formation) at a site of tissue damage in the upper respiratory tract or ear of a patient comprising administering to a patient in need thereof at the site of tissue damage, an amount of liposomes sufficient to suppress undesired tissue formation or to restore the original appearance of the tissue (or suppress scar tissue), said liposomes containing povidone iodine. In view of the amendments to the claims, Applicants respectfully submit that the current Section 112, first paragraph, rejection is thus obviated.

Moreover, Applicants note that the currently claimed invention is fully meets all requirements of Section 112, first paragraph. As taught in the specification at page 6, the generation of new body tissue after a wound can sometimes have a negative effect in that the regrown tissue, scar tissue, does not have the same characteristics of the damaged or destroyed tissue it replaces. Additionally, the scar tissue that can form can also be disfiguring. The methods of the invention are directed to the suppression of the growth of such scar tissue.

Applicants invite the Examiner's attention to Vogt *et al.*, 2001, Wound Rep. Reg. 9:116-122 ("Vogt"); Reimer *et al.*, 2000, Dermatology 201:235-241 ("Riemer"), and Integrated Final Study Report for HOM3401, Efficiency and Tolerability of PVP-iodine-liposome-hydrogel (Hydrosom) in the treatment of acute transplantation wounds by Prof. Dr. P. Vogt, May 8, 2003 ("Final Study"), which are made of record in the Supplemental Information Disclosure Statement submitted concurrently herewith. Vogt discloses a comparative study between the effects of a hydrogel formulation of liposomes containing povidone iodine and chlorohexidine gauze administration to patients receiving meshed skin grafts after burns or reconstructive procedures. The results of the study showed that wounds treated with the povidone iodine containing liposome formulation showed less graft loss, earlier epithelialization and better healing of the wounds than those wounds treated with the conventional gauze. See, the Abstract of Vogt. Further, Vogt discloses on page 119, left column, that control treatment of the graft site resulted in significant formation of scabs in the mesh holes, whereas those grafts treated with liposomes containing povidone iodine resulted in a clean and smooth surface almost without scab formation.

Reimer discloses the results of an proof of concept phase II study wherein primary wounds of different origin were treated with a hydrogel formulation of liposomes containing povidone iodine and compared to treatment with povidone iodine alone. As discussed on page

240, left column, the results indicated that the graft take rate appeared to be improved and the wounds closed more rapidly. The Final Study summarizes the results of a clinical trial of wound treatment with a povidone iodine liposome hydrogel and fat gauze as compared to treatment with a fat gauze alone. The results of the trial clearly showed that treatment with the povidone iodine liposome hydrogel results in better wound healing and significant less transplant losses. Final Study, page 95.

Applicants submit that the experimental evidence in Vogt, Reimer and The Final Study showing the promotion of wound healing and suppression of undesired tissue growth by liposomes containing povidone iodine would be predictive to one of skill in the art that liposomes containing povidone iodine can suppress undesired tissue formation or restore the original appearance of tissue at the site of tissue damage in the upper respiratory tract and/or ear. This conclusion is supported by Dr. Wolfgang Fleischer, a co-inventor of the present application in his Declaration under 37 C.F.R. § 1.132 ("Declaration"). The Examiner's attention is invited to Paragraph 14 of the Declaration, in which Dr. Fleischer states:

> It is my opinion as a skilled artisan that the foregoing experimental evidence showing the promotion of wound healing and suppression of undesired tissue growth by liposomes containing povidone iodine would be predictive to one of skill in the art that liposomes containing povidone iodine can suppress undesired tissue formation or restore the original appearance of tissue at the site of tissue damage in the upper respiratory tract or ear. It is also my opinion as a skilled artisan that one skilled in the art would have no reason to doubt that a composition which suppresses undesired tissue formation in the epidermis and underlying epithelial cell layer would not also suppress undesired tissue formation in the upper respiratory tract and/or ear.

Applicants submit that the foregoing clearly demonstrates that treating damaged tissue, *i.e.*, a wound, with liposomes containing povidone iodine results in a greater rate of epithelialization, fewer losses of grafts and less scab formation, which are each indicative of suppressing undesired tissue formation as well as restoring the original appearance of tissue at a site of tissue damage. Therefore, Applicants respectfully submit that the claimed method of suppressing undesired tissue formation or restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract and/or ear is fully enabled by the specification.

2. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 26, 29, 33, 38, 39, 44, 45 and 47 are rejected under 35 U.S.C. § 112, second paragraph, allegedly, as being indefinite for failing to particularly point out and distinctly claims the subject matter which is regarded as the invention.

In view of the cancellation of claims 26, 29, 33, 38, 39, 44, 45 and 47, Applicants submit that these Section 112, second paragraph, rejections have been obviated, and, thus, Applicants request their withdrawal.

3. Double Patenting

Claims 25, 26, 29-47 and 51-53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 22-24, 26-43 and 51-57 of co-pending Application Serial No. 08/701,450.

In response, Applicants note that since the double patenting rejection is provisional, it will be addressed once allowable subject matter has been indicated in this or the referenced application. Thus, Applicants respectfully request that the Examiner hold this provisional rejection in abeyance until there is an indication of allowable subject matter.

4. Rejection under 35 U.S.C. § 102(b)

Claims 25, 26, 35-39, 43, 46 and 51-53 are rejected under 35 U.S.C. § 102(b), allegedly, as anticipated by U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight"). Applicants disagree and point out that the claims as amended are not anticipated by Knight.

As discussed above, the claims as pending are directed to methods for suppressing undesired tissue formation, *e.g.*, suppressing scar formation, at a site of tissue damage in the upper respiratory tract or ear by administering liposomes containing povidone iodine to the site of tissue damage. Knight discloses small aqueous aerosol droplets containing liposomes, wherein such liposomes are interacted with drugs, and their use in treating medical conditions in the lungs. No where does Knight disclose liposomes containing povidone iodine, or that such liposomes containing povidone iodine can be used for suppressing undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract or ear. Moreover, Knight does not teach or suggest that the liposomes can be interacted with compounds that are not drugs. See Tables 1-2 of Knight. Povidone iodine is an aggressive oxidizing antiseptic, not a drug such as an antibiotic, anti-viral or anti-fungal drug.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed . . ." *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). Not only does Knight not disclose liposomes containing povidone iodine, but Knight also does not disclose a method according to the present invention for suppressing

undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract or ear.

In view of the foregoing, Applicants respectfully submit that this Section 102 rejection is in error and request its withdrawal.

5. Rejection under 35 U.S.C. § 103

Claims 25, 26, 29-47 and 51-53 are rejected under 35 U.S.C. § 103(a), allegedly, as obvious over European Patent No. 639373 ("the '373 patent") by itself or in view of U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight").

Applicants disagree and respectfully submit that this Section 103 rejection is improper. A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). As explained in detail below, not only is there no suggestion or motivation in the prior art to use iodine compounds in wound healing, there also is no suggestion or motivation to administer iodine compounds to internal body tissues, including respiratory tract tissue.

As explained in Paragraph 5 of the Declaration of Dr. Wolfgang Fleischer ("the Declaration") submitted concurrently herewith, the aim of wound treatment is generally to keep the number of microorganisms in the wound as low as possible in order to prevent infection and sepsis, and at the same time, to stimulate the repair process in order to achieve optimum healing and quality of wound closure, including restoring the tissue at the wound site to its original appearance and function. However, agents that stimulate healing, which are largely based on maintaining moisture content, are usually contraindicated in the presence of a potential infection since moist treatment of wounds increases risk of bacterial infection. Additionally, antiseptics and antibiotics are mostly inhibitory to granulation or epithelialization. Thus, Dr. Fleischer concludes that there has been a need in the art for treatments to both stimulate wound healing and prevent infection without inhibiting the other.

The '373 patent teaches that liposomes containing povidone iodine can be administered externally, *i.e.*, to the skin or eye, for treatment of an infection. Further, the '373 patent teaches that when liposomes containing povidone iodine also contain a wound healing promoting agent, such liposomes can be used to treat an infection and to promote wound healing. According to Dr. Fleischer in ¶ 6 of the Declaration, a person of ordinary skill in the art, upon reading the '373 patent, would recognize that in order to promote the healing of an external wound, liposomes containing a wound healing promoting agent need to be administered to the site of the wound. The '373 patent discloses on page 3, line 15 that such wound healing promoting agents include compounds such a vitamins, allantoin and some azulenes. Thus, the '373 patent teaches that promoting wound healing is not the result of the application of liposomes containing povidone iodine, but, rather, is the result of the application of liposomes also containing a wound healing promoting agent. There is no disclosure in the '373 patent that teaches or suggests that liposomes containing povidone iodine can be used without a wound healing promoting agent for promoting the healing of wounds. See also the Declaration at ¶¶ 6 and 15.

Not only is there no teaching in the '373 patent that liposomes containing iodine without a wound healing promoting agent can be administered to promote wound healing, the prior art actually taught away from using iodine compounds in wound healing because it had been shown that iodine compounds interfered with wound healing. The Examiner's attention is invited to the Declaration at ¶ 7, where Dr. Fleischer explains that it was well known prior to the filing of the present application that iodine and iodine-containing compounds such as povidone iodine are highly oxidizing agents that have been used as topical disinfectants and anti-infectants. Dr. Fleischer further explains that it was also well known in the art that iodine and iodine compounds can adversely effect wound healing. As evidence, Dr. Fleischer refers to Lineaweaver *et al.*, 1985, Arch Surg 120:257-270, (disclosing that povidone iodine significantly retarded wound healing) and to Kallenberger *et al.*, 1991, Hyg + Med 16:383-395 (disclosing that application of antiseptics, such as the iodophores Braunol® and Betadine®, significantly reduced proliferation rates of epithelial cells). In view of the teachings of the prior art, Dr. Fleischer concludes that "a skilled artisan would not have been motivated to apply iodine compounds to external wounds in order to enhance wound healing."

Further, Applicants point out that there is no teaching or suggestion in the '373 patent that the liposomes containing povidone iodine could be administered to any other part of the body other than to external parts of the body, such as the skin and the mucous membrane of the eye. Upon reading the '373 patent in its entirety, *i.e.*, as a whole, it is clear that there is no teaching or suggestion to administer the liposomal formulation of povidone iodine and a wound

healing promoting agent to an internal body part. A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 449 U.S. 851 (1984). The specification consistently teaches that the formulations are for external application, such as treatment of an eye infection or treatment of an external wound, not to internal areas of the body. Applicants note that the mucosa of the eye is not considered an internal tissue.

Moreover, the prior art taught actually away from application of an antiseptic agent like povidone iodine to more sensitive internal tissue, especially respiratory tract tissue, due to the known harsh oxidizing nature of iodine and the knowledge that iodine can damage and/or kill cells. As Dr. Fleischer explains in ¶ 8 of the Declaration, much of the tissue in the upper and lower respiratory tract is lined with ciliated cells, which cells are required for proper lung function. The cilia on the lung cells move (beat) in unison (frequency around 16 hz) to expel mucous and contaminants from the lungs. Where the cilia do not function properly, lung function is impaired and can lead to disease and death. Cystic fibrosis is one exemplary disease resulting from non-functioning cilia. Dr. Fleischer states that "[i]n view of the importance of not harming ciliated cells and in view of the known ability of iodine compounds to damage cells, one skilled in the art would not have been motivated to apply iodine compounds to the respiratory tract for any reason for fear of damaging the ciliated cells." Declaration at ¶ 8. Applicants submit that not only is there no suggestion or teaching in the '373 patent to administer liposomal formulations of povidone iodine to respiratory tract tissue, the prior art did not provide a reasonable expectation of success since the art taught away from administering liposomal formulations of povidone iodine to respiratory tract tissue.

Knight does not fill in the gap between the claimed invention and the disclosure of the '373 patent. Knight discloses small aqueous aerosol droplets containing liposomes and wherein such liposomes are interacted with drugs, and their use in treating medical conditions in the lungs. No where does Knight teach, much less, suggest that such liposomes can be used for suppressing undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the respiratory tract. Moreover, Knight does not teach or suggest that the liposomes can be interacted with povidone iodine, which is an aggressive oxidizing antiseptic, not a drug such as an antibiotic. The Examiner is invited to ¶ 16 of the Declaration, where Dr. Fleischer states that he has reviewed the Knight reference and that Knight discloses that liposomes can be administered to the respiratory tract. Dr. Fleischer continues that it is his belief that none of the compounds that are taught to be formulated with liposomes in Knight is in

the same class of compounds as povidone iodine, which is a highly oxidative chemical antiseptic agent. Dr. Fleischer concludes that it is his belief that administration of the liposomal formulations of Knight are not suggestive of administration of liposomal formulations of povidone iodine to the upper respiratory tract and/or non-external parts of the ear because the compounds formulated with liposomes by Knight are not in the same class of compounds to which povidone iodine belongs.

There is nothing in the '373 patent or in Knight, alone or in combination, that teaches or suggest that liposomes containing povidone iodine alone can be used to suppress undesired tissue formation or for restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract. Further, since the prior art teaches away the administration of iodine compounds for the purpose of wound healing, as well as teaches away the administration of iodine compounds to an interior part of the body for any reason, the Examiner has not provided the required reasonable expectation of success in achieving the claimed methods. Thus, Applicants respectfully submit that the Section 103 rejection is in error and must be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 326-3921 if any questions or issues remain.

Respectfully submitted,

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